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Prevalence and clinical implications of valvular calcification on coronary computed tomography angiography

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Aims

Valvular heart disease can be identified by calcification on coronary computed tomography angiography (CCTA) and has been associated with adverse clinical outcomes. We assessed aortic and mitral valve calcification in patients presenting with stable chest pain and their association with cardiovascular risk factors, coronary artery disease, and cardiovascular outcomes.

Methods and results

In 1769 patients (58 ± 9 years, 56% male) undergoing CCTA for stable chest pain, aortic and mitral valve calcification were quantified using Agatston score. Aortic valve calcification was present in 241 (14%) and mitral calcification in 64 (4%). Independent predictors of aortic valve calcification were age, male sex, hypertension, diabetes mellitus, and cerebrovascular disease, whereas the only predictor of mitral valve calcification was age. Patients with aortic and mitral valve calcification had higher coronary artery calcium scores and more obstructive coronary artery disease. The composite endpoint of cardiovascular mortality, non-fatal myocardial infarction, or non-fatal stroke was higher in those with aortic [hazard ratio (HR) 2.87; 95% confidence interval (CI) 1.60–5.17; $P < 0.001$] or mitral (HR 3.50; 95% CI 1.47–8.07; $P = 0.004$) valve calcification, but this was not independent of coronary artery calcification or obstructive coronary artery disease.

Conclusion

Aortic and mitral valve calcification occurs in one in six patients with stable chest pain undergoing CCTA and is associated with concomitant coronary atherosclerosis. Whilst valvular calcification is associated with a higher risk of cardiovascular events, this was not independent of the burden of coronary artery disease.

Keywords

aortic valve • mitral valve • computed tomography • computed tomography coronary angiography

Introduction

Valvular heart disease is an important cause of morbidity and mortality worldwide and shares similar risk factors with coronary artery disease.¹ Incidental calcification of the aortic or mitral valve on

computed tomography (CT) may identify patients with previously undiagnosed valvular heart disease. Coronary CT angiography (CCTA) is now a widely used non-invasive imaging modality, frequently the first-line investigation for patients with suspected coronary artery disease.^{2,3} Therefore, the identification of incidental

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where required. Surgical coding information was used to identify patients who underwent aortic or mitral valve surgery using the OPCS (Office of Population Censuses and Surveys) 4 Classification of Surgical Operations and Procedures.

Statistical analysis

The primary composite endpoint of this sub-study was cardiovascular mortality, non-fatal MI, or non-fatal stroke. Quantitative data are presented as mean and standard deviation or, if the data were not normally distributed, median and interquartile intervals. Statistical significance was assessed using Pearson's χ^2 test, Fisher's exact test, Students *t*-test, or Mann–Whitney *U* test, as appropriate. Correlations were assessed using Spearman's rank order correlation (0–0.19 very weak, 0.2–0.39 weak, 0.40–0.59 moderate, 0.6–0.79 strong, and 0.8–1 very strong). Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented. Ordinal regression analysis was performed to assess the effect of cardiovascular risk factors on aortic and mitral valve calcification. Multivariable analysis was performed including valvular calcification, coronary artery calcification, and the presence of obstructive coronary artery disease. Outcome data were analysed using Cox proportional hazards regression and presented graphically using cumulative incidence plots of the time to the first event. Statistical analysis was performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria). A statistically significant difference was defined as a two-sided *P*-value <0.05.

Results

Study population

Of the 4146 patients recruited into the study, 2073 were randomized to CT and 1769 CT scans were available and of suitable quality for analysis. Valvular calcification (Table 1) was identified in 273 (15%) patients, with aortic valve calcification occurring in 241 (14%) patients, mitral calcification in 64 (4%) patients, and combined aortic and mitral calcification in 32 (2%) patients. After 4.82 ± 1.13 years of follow-up, 53 patients had met the composite endpoint: cardiovascular mortality ($n = 4$), non-fatal MI ($n = 38$), or non-fatal stroke ($n = 11$).

Aortic valve calcification

Independent predictors of the presence of aortic valve calcification (Figure 2) were age [odds ratio (OR) 1.11; 95% CI 1.08–1.15; $P < 0.001$], male sex (OR 2.62; 95% CI 1.87–3.70; $P < 0.001$), hypertension (OR 1.39, 95% CI 1.02–1.88; $P = 0.037$), diabetes mellitus (OR 1.81; 95% CI 1.09–2.97; $P = 0.020$), and a prior history of cerebrovascular disease (OR 2.30; 95% CI 1.32–3.96; $P = 0.003$).

Patients with aortic valve calcification had a higher coronary artery calcium score [390 (interquartile range, IQR 61–1105) Agatston units (AU)] compared to those without aortic valve calcification [8 (IQR 0–145) AU, $P < 0.001$, [Figure 3](#)]. Patients with aortic valve calcification

Table 1 Characteristics of study participants

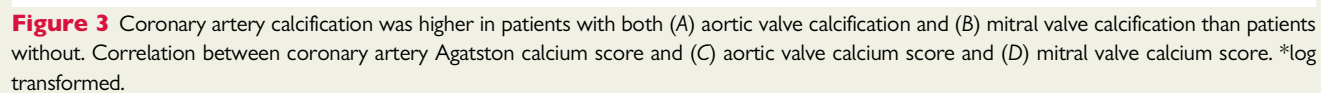
	All participants	Aortic valve calcification		Mitral valve calcification	
			P-value		P-value
N	1769	241 (14%)		64 (4%)	
Male	997 (56%)	178 (74%)	<0.001	41 (64%)	0.206
Age (years)	58 ± 9	64 ± 7	<0.001	65 ± 7	<0.001
Body mass index (kg/m ²)	30 ± 6	30 ± 5	0.896	30 ± 5	0.386
Atrial fibrillation	34 (2%)	7 (3%)	0.213	2 (3%)	0.350
Smoking status					
Current smoker	330 (19%)	37 (15%)	0.007	5 (8%)	0.007
Ex-smoker	593 (34%)	102 (42%)		32 (50%)	
Non-smoker	845 (48%)	102 (42%)		27 (43%)	
Hypertension	608 (35%)	122 (51%)	<0.001	36 (57%)	<0.001
Diabetes Mellitus	196 (11%)	45 (19%)	<0.001	14 (22%)	0.005
Family history CHD	765 (45%)	91 (38%)	0.048	20 (32%)	0.053
Previous CHD	178 (10%)	39 (16%)	<0.001	11 (17%)	0.054
Previous PAD	31 (2%)	7 (3%)	0.178	1 (2%)	1
Previous CVD	79 (4%)	27 (11%)	<0.001	6 (10%)	0.059
Total cholesterol concentration (mg/dL)	192 ± 73	179 ± 74	0.003	182 ± 85	0.324
Anginal symptoms					
Typical angina	654 (37%)	124 (51%)	<0.001	33 (52%)	0.046
Atypical angina	432 (24%)	66 (27%)		11 (17%)	
Non-anginal	683 (39%)	51 (21%)		20 (31%)	
Risk score	17.9 ± 11.0	24.6 ± 11.1	<0.001	25.5 ± 11.5	<0.001

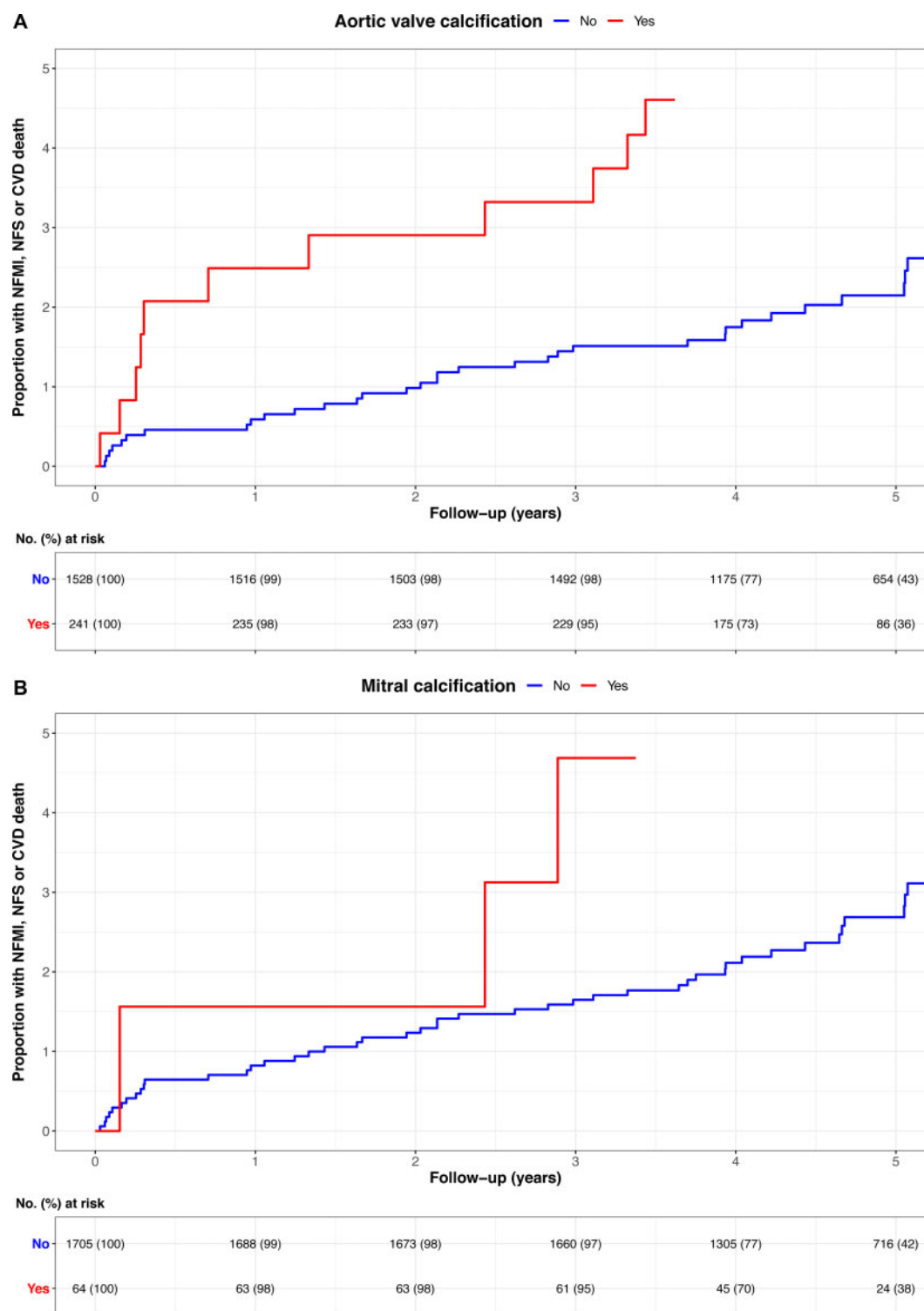
Data are presented as N (%), mean \pm standard deviation, or median (interquartile range).

P-values represent comparison to total cohort.

CHD, coronary heart disease; CTCA, computed tomography coronary angiography; CVD, cerebrovascular disease; PAD, peripheral arterial disease.

Bold values indicate statistical significance.





patients with coronary artery disease had valvular heart disease. Thus, the presence of valvular heart disease could be a trigger to assess the coronary arteries, but the presence of coronary artery disease is not an indication for valvular assessment with echocardiography.

Our study has several limitations. This includes the small number of clinical events and that patients were managed according to routine clinical practice rather than having management prescribed on the basis of the imaging findings. The prevalence of valvular calcification and cardiovascular risk factors varies depending on the cohort studied. The age range of the SCOT-HEART population meant that mild calcification was the most common pathology and that the 5-year duration of follow-up might not have been sufficient for this early stage of disease to result in clinical events. In addition, the SCOT-HEART participants were recruited from cardiology outpatient clinics with suspected angina due to coronary artery disease. Although two-thirds of the patients were ultimately diagnosed as not having angina due to coronary artery disease, these results may not be representative of asymptomatic patients or the general population. Finally, we do not have data on the progression of valve calcification in this cohort which in other studies appears unrelated to cardiovascular risk factors but is most closely associated with the severity of baseline valve disease and calcification.

Conclusion

Valvular calcification is a frequent incidental finding on CCTA and is associated with cardiovascular risk factors and the presence of coronary artery disease. Whilst patients with aortic or mitral valve calcification demonstrate a three-fold increased risk of future adverse cardiovascular events, this appears to be mediated by co-existent coronary artery disease.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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References

1. d'Arcy JL, Coffey S, Loudon MA, Kennedy A, Pearson-Stuttard J, Birks J et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. *Eur Heart J* 2016;**37**:3515–22.
2. National Institute for Health and Clinical Excellence. Chest Pain of Recent Onset: Assessment and Diagnosis of Recent Onset Chest Pain or Discomfort of Suspected Cardiac Origin. Clinical Guideline 95. NICE, London 2016.
3. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: the Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J* 2019;**41**:407–77.
4. Barasch E, Gottdiener JS, Marino Larsen EK, Chaves PH, Newman AB. Cardiovascular morbidity and mortality in community-dwelling elderly individuals with calcification of the fibrous skeleton of the base of the heart and atherosclerosis (The Cardiovascular Health Study). *Am J Cardiol* 2006;**97**:1281–6.
5. Kizer JR, Wiebers DO, Whisnant JP, Galloway JM, Welty TK, Lee ET et al. Mitral annular calcification, aortic valve sclerosis, and incident stroke in adults free of clinical cardiovascular disease: the Strong Heart Study. *Stroke* 2005;**36**:2533–7.
6. Fox CS, Vasan RS, Parise H, Levy D, O'Donnell CJ, D'Agostino RB et al. Mitral annular calcification predicts cardiovascular morbidity and mortality: the Framingham Heart Study. *Circulation* 2003;**107**:1492–6.
7. Clavel MA, Pibarot P, Messika-Zeitoun D, Capoulade R, Malouf J, Aggarwal S et al. Impact of aortic valve calcification, as measured by MDCT, on survival in patients with aortic stenosis: results of an international registry study. *J Am Coll Cardiol* 2014;**64**:1202–13.
8. Cowell SJ, Newby DE, Burton J, White A, Northridge DB, Boon NA et al. Aortic valve calcification on computed tomography predicts the severity of aortic stenosis. *Clin Radiol* 2003;**58**:712–6.
9. Liu F, Coursey CA, Grahame-Clarke C, Sciacca RR, Rozenshtein A, Homma S et al. Aortic valve calcification as an incidental finding at CT of the elderly: severity and location as predictors of aortic stenosis. *Am J Roentgenol* 2006;**186**:342–9.
10. Koos R, Kuhl HP, Muhlenbruch G, Wildberger JE, Gunther RW, Mahnken AH. Prevalence and clinical importance of aortic valve calcification detected incidentally on CT scans: comparison with echocardiography. *Radiology* 2006;**241**:76–82.
11. Clavel MA, Messika-Zeitoun D, Pibarot P, Aggarwal SR, Malouf J, Araoz PA et al. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler echocardiographic and computed tomographic study. *J Am Coll Cardiol* 2013;**62**:2329–38.
12. Pawade T, Clavel MA, Tribouilloy C, Dreyfus J, Mathieu T, Tastet L et al. Computed tomography aortic valve calcium scoring in patients with aortic stenosis. *Circ Cardiovasc Imaging* 2018;**11**:e007146.
13. Falk V, Baumgartner H, Bax JJ, De Bonis M, Hamm C, Holm PJ et al.; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur J Cardiothorac Surg* 2017;**52**:616–64.
14. Labovitz AJ, Nelson JG, Windhorst DM, Kennedy HL, Williams GA. Frequency of mitral valve dysfunction from mitral annular calcium as detected by Doppler echocardiography. *Am J Cardiol* 1985;**55**:133–7.
15. Massera D, Trivieri MG, Andrews JPM, Sartori S, Abgral R, Chapman AR et al. Disease activity in mitral annular calcification. *Circ Cardiovasc Imaging* 2019;**12**:e008513.
16. Lancellotti P, Magne J, Dulgheru R, Clavel M-A, Donal E, Vannan MA et al. Outcomes of patients with asymptomatic aortic stenosis followed up in heart valve clinics. *JAMA Cardiol* 2018;**3**:1060–8.
17. Di Minno MND, Poggio P, Conte E, Myasoedova V, Songia P, Mushtaq S et al. Cardiovascular morbidity and mortality in patients with aortic valve calcification: a systematic review and meta-analysis. *J Cardiovasc Comput Tomogr* 2019;**13**:190–5.
18. Newby DE, Williams MC, Flapan AD, Forbes JF, Hargreaves AD, Leslie SJ et al. Role of multidetector computed tomography in the diagnosis and management of patients attending the rapid access chest pain clinic, The Scottish computed tomography of the heart (SCOT-HEART) trial: study protocol for randomized controlled trial. *Trials* 2012;**13**:184.
19. SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet* 2015;**385**:2383–91.

20. SCOT-HEART Investigators, Newby DE, Adamson PD, Berry C, Boon NA, Dweck MR et al. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med* 2018;**379**:924–33.
21. Williams MC, Hunter A, Shah ASV, Assi V, Lewis S, Smith J et al. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. *J Am Coll Cardiol* 2016;**67**:1759–68.
22. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;**15**:827–32.
23. Willemink MJ, Takx RA, Isgum I, de Koning HJ, Oudkerk M, Mali WP et al. Prognostic value of heart valve calcifications for cardiovascular events in a lung cancer screening population. *Int J Cardiovasc Imaging* 2015;**31**:1243–9.
24. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. *N Engl J Med* 1999;**341**:142–7.
25. Owens DS, Budoff MJ, Katz R, Takasu J, Shavelle DM, Carr JJ et al. Aortic valve calcium independently predicts coronary and cardiovascular events in a primary prevention population. *JACC Cardiovasc Imaging* 2012;**5**:619–25.
26. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol* 1997;**29**:630–4.
27. Eveborn GW, Schirmer H, Lunde P, Heggelund G, Hansen JB, Rasmussen K. Assessment of risk factors for developing incident aortic stenosis: the Tromso Study. *Eur J Epidemiol* 2014;**29**:567–75.
28. Yan AT, Koh M, Chan KK, Guo H, Alter DA, Austin PC et al. Association between cardiovascular risk factors and aortic stenosis: the CANHEART Aortic Stenosis Study. *J Am Coll Cardiol* 2017;**69**:1523–32.
29. Gondrie MJ, van der Graaf Y, Jacobs PC, Oen AL, Mali WP; On behalf of the PROVIDI Study Group. The association of incidentally detected heart valve calcification with future cardiovascular events. *Eur Radiol* 2011;**21**:963–73.
30. Atar S, Jeon DS, Luo H, Siegel RJ. Mitral annular calcification: a marker of severe coronary artery disease in patients under 65 years old. *Heart* 2003;**89**:161–4.
31. Barasch E, Gottdiener JS, Larsen EK, Chaves PH, Newman AB, Manolio TA. Clinical significance of calcification of the fibrous skeleton of the heart and atherosclerosis in community dwelling elderly. The Cardiovascular Health Study (CHS). *Am Heart J* 2006;**151**:39–47.